Robust generation of induced pluripotent stem cells by a potent set of engineered factors

Grant Award Details

Robust generation of induced pluripotent stem cells by a potent set of engineered factors

Grant Type: Tools and Technologies II

Grant Number: RT2-01942

Project Objective: The goal of this project is to engineer reprogramming factors to be more potent transcriptional transactivators, and to use them for the robust generation of iPSC.

Investigator:

Name:	Jifan Hu
Institution:	GMR Epigenetics
Type:	PI

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,356,052

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Robust generation of induced pluripotent stem cells by a potent set of engineered factors

Public Abstract: The recent discovery of iPSC (induced Pluripotent Stem Cell) technology marks a promising breakthrough in regenerative medicine. The beauty of the technology is its ability to convert adult mature cells into embryonic stem cells through the expression of a cocktail of essential factor genes. Thus, iPSCs bypass the ethical dilemma of using embryonic materials and eggs. In addition, the creation of iPSCs for individual patients using their own cells can avoid immune rejection and achieve successful therapeutic effects. Since its initial discovery, the method has been used to generate patient-specific stem cells for regenerative therapy and drug screening, including Parkinson disease, sickle cell anemia, Huntington disease and many other genetic diseases. It is predicted that patients may someday be treated with their own healthy versions of stem cells.

The technology of iPSC induction, however, is in its infancy. Generation of iPS cells depends on the synthesis of factor proteins that regulate the developmental clock of adult cells in order to return them to the embryonic state. Viruses are a common approach to deliver factor genes into the cell but they incur the risks of gene mutation and instability. Most critically, the efficiency of iPSC induction is extremely low with all existing approaches. Without clearing these road blocks, it would be impossible to translate this technology to the clinic in the near future.

In this project, we propose to fundamentally improve this technology by re-engineering the iPS-inducing factors. We will modify part of these factor proteins, which function inefficiently, to become highly potent in activating target genes related to stemness. By functional screening, we will identify the most potent set of factors for iPSC induction. In addition, we have identified a novel iPS-inducing factor in our lab. Together with those engineered factors, we will work out an ideal cocktail of factors that robustly induce iPSCs. To make virus-free iPS cells, we have developed an enzyme that specifically recognizes and removes the virus-delivered factor genes in the host cell. The removal of the viral transgene will avoid tumor formation and increase clinical safety. Finally, we will generate the safest, genetic material-free stem cells directly by using proteins produced by the genes of engineered factors.

With these approaches, the generation of iPSCs will be much more robust, enabling us to create patient-specific stem cells efficiently and safely within a short period of time. We will be the first to break the current technical bottleneck by modifying their protein structure. Taken together, this project may ultimately revolutionize the existing ways to create genetically tailored stem cell lines for research and disease treatment in regenerative medicine.

Statement of Benefit to California:

Induced pluripotent stem cells (iPSCs) offer hope and promise for the therapeutic usage of personalized stem cell in regenerative medicine. Among ten leading death causes in California, five of them can directly benefit from cell-based tissue regeneration, including heart disease, stroke, Alzheimer's disease, diabetes, and liver diseases. Currently, the economic burdens derived from these diseases are enormous. It is estimated from State of California, Department of Public Health that California taxpayers pay 48 billion annually for cardiovascular diseases, 73 billion excluding non-paid family care for Alzheimer's disease, and 116 billion for diabetes-related diseases.

By far, personated iPSC lines have been successfully made from patients with a variety of diseases, including Alzheimer's disease, Parkinson disease, sickle cell anemia, Huntington disease, muscular dystrophy and many other genetic diseases. It is hoped that these patients may someday be treated with their own healthy versions of stem cells. However, the iPSC technology still has several shortcomings inhibiting its clinical application. Our proposed research aims at improving this technology by revolutionizing existing methods in producing iPSCs and freeing them from cancer-causing side-effects. This research will finally lead to a new way of developing personalized stem cells for therapy and possibly a cure to above mentioned diseases.

The goal of this study is to robustly produce iPSCs that are safe for therapeutic applications. It is thus in line with the mission of the California Institute for Regenerative Medicine – to promote rapid progress in stem cell research leading to treatments and cures for diseases and to the growth of a stem cell and regenerative medicine industry critical to future clinical applications.

Our proposed improvements in the production of iPSCs, when translated into therapeutic interventions, will directly benefit the health of California citizens and reduce the economic burden presently borne by California taxpayers. Indirectly, we believe this research will increase California's visibility in stem cells research, attract more federal funding to sponsor future research and fulfill the wish of California citizens who voted to support stem cell research. It may also stimulate California's economy growth by stimulating the iPSC regenerative medicine industry for the treatment or cure of diseases.

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